REMARKS

Paragraph numbers below refer to the Substitute Specification (clean copy) filed on April 3, 2008.

Claims 1–16, 18 and 20–25 are pending in the present application. Claims 17 and 19 were canceled in an earlier amendment.

Claim 1 is amended to more clearly indicate that the cement matrix comprises a hot-meltable adhesive in which the active substance is dispersed and partly or completely dissolved and melted using a hot-melt process. Hot-melt processes where rotigotine is partly or completely dissolved and melted are illustrated in the original specification as filed, including paragraphs **[0034]** and **[0107]–[0113]**.

Claim 14 is amended to change its dependency from Claim 1 to Claim 12 to more clearly indicate features for attaining the release profiles of Claims 14 and 15.

No increase in total claim number or in number of independent claims results from the present amendment, no additional claim fees are believed payable, no new matter is added and no change in inventorship results from the present amendment.

RESPONSE TO OFFICE ACTION DATED JUNE 24, 2008

1. Obviousness-type double patenting

Claims 1–16, 18 and 20–25 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 28–59 of co-pending application Serial No. 10/523,908.

The rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the co-pending application issues as a patent.

2. Rejections under 35 U.S.C. §112, first paragraph

2.1. Claims 14 and 15

Claims 14 and 15 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabling for the release profiles recited. This rejection is respectfully traversed.

By amendment herein, Claim 14 is currently amended as to dependency, and now incorporates all limitations of Claim 12 as well as of Claim 1. The TTS of Claim 14

comprises a cement matrix that comprises a hot-meltable adhesive in which rotigotine is dispersed and partly or completely dissolved and melted using a hot-melt process, as recited in Claim 1 and enabled by the specification at least at paragraphs **[0034]** and **[0107]–[0113]**. The cement matrix more particularly comprises (a) 50–99 weight % of a hot-meltable adhesive, (b) 4–40 weight % of rotigotine, (c) 0–40 weight % of an internal-phase component, and (d) 0–10 weight % of other adjuvants, as recited in Claim 12 and enabled by the specification at least at paragraph **[0101]**. Claims 14 and 15 recite that upon application to human skin, a TTS as described above induces an average plasma concentration of 0.4 to 2 ng/ml rotigotine for a period of at least 5 or at least 7 days, respectively. Types and amounts of materials embraced by Claim 12 are stated in the specification at paragraphs **[0080]–[0086]** to provide flux rates consistent with achieving plasma concentrations of 0.4 to 2 ng/ml rotigotine in the patient for a period of at least 5 days (Claim 14) or at least 7 days (Claim 15).

The flux rate of a TTS constructed according to Claim 12 is readily ascertained by a person of ordinary skill in the art in view of the original specification as filed. For example, the referenced *in vitro* model of Tanojo (1997) J. Controlled Release 45:41–47 is identified as a good model for predicting *in vivo* flux rate as determined in clinical studies. See specification, paragraphs **[0088]–[0097]**; Fig. 6b; and Example 9, paragraphs **[0151]–[0152]**. Based on the Tanojo reference and illustrated examples in the specification, one of skill in the art can readily test any TTS falling within the scope of Claim 12 and determine whether it meets the functional limitations recited in Claims 14 or 15; *i.e.*, 0.4–2 ng/ml average plasma concentration over a 5-day or 7-day period respectively. Such determination does not require undue experimentation and the specification provides adequate guidance to determine if a TTS constructed according to Claim 12 meets the necessary functional criteria of Claims 14 or 15. As admitted in the present Action (p. 5), the level of skill in the art is very high.

Withdrawal of the present rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

2.2. Claim 10

Claim 10 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement of that paragraph. This rejection is respectfully traversed.

Claim 10 is written in Markush form in which the linking conjunction "and" is proper. Paragraph **[0076]** of the specification as filed discloses options for the internal-phase components including

(a) hydrophilic or amphiphilic polymers,

(b) hydrophilic or amphiphilic copolymers,

(c) mixtures of (a) and/or (b) with pharmaceutically acceptable softeners,

etc.

These components are properly recited in Claim 10 as "selected from the group consisting of (a) hydrophilic and amphiphilic polymers and mixtures thereof with pharmaceutically acceptable softeners, (b) hydrophilic and amphiphilic copolymers and mixtures thereof with pharmaceutically acceptable softeners," *etc.* Nothing in the present specification limits the meaning of the conjunction "or" as used in paragraph **[0076]** to exclude the presence of both hydrophilic and amphiphilic types; likewise "an internal-phase component selected from the group consisting of hydrophilic and amphiphilic" types is to be read as a proper Markush recitation in which either one of the two types, or both, is present.

Withdrawal of the present rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

3. Rejection under 35 U.S.C. §103(a)

Claims 1–16, 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,807,570 ("Chen"), in view of Metman *et al.* (2001) Clin. Neuropharmacol. 24:163–169 ("Metman") and U.S. Patent No. RE 36,754 ("Noel"). This rejection is respectfully traversed for reasons detailed below.

The combination of the Chen, Metman, and Noel references, even if such combination can properly be made, which is not admitted herein, cannot establish a *prima facie* case of obviousness for independent Claims 1, 18 and 20 since in each case the combination is missing all of the claimed features. See *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (combined references must teach or suggest all the claim limitations to establish a *prima facie* case of obviousness). In particular, the cited combination fails to teach the present hot-melt process wherein rotigotine is dispersed and partly or completely dissolved and melted to form the resultant cement matrix found in the transdermal therapeutic system

(TTS) of Claim 1 and which is used in the methods of Claims 18 and 20. Moreover, no apparent reason based either on the references themselves or the general knowledge in the art is provided by which a skilled artisan would be led to include the missing subject matter. See *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (obviousness includes determining whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue). The claims are not obvious and are patentable over the cited combination of references, as explained in greater detail below.

3.1. Claims 1–16

Claim 1 is drawn to a TTS comprising an active-substance-containing cement matrix. The cement matrix comprises a hot-meltable adhesive in which the active substance rotigotine is dispersed and partly or completely dissolved and melted using a hot-melt process. Applicants have surprisingly found that, after melting, rotigotine remains stable in a variety of matrices even without the addition of stabilizers or antioxidants. HPLC measurements with UV analyses at 220 nm and 272 nm showed that, even without the admixture of antioxidants, the purity level of the active substance routinely remained above 98% and generally better than 99% (see specification, Table 24; Examples 4, 6 and 7; and paragraph **[0108]**). For example, rotigotine is introduced into the matrix either premelted or by metering it in solid form into the hot matrix melt where it is melted. Paragraph **[0110]**. Either way, the rotigotine is infused and dispersed within the cement matrix. Paragraph **[0109]**.

In contrast, the primary reference, Chen, does not teach a hot-meltable adhesive in which the active substance rotigotine is dispersed and partly or completely dissolved and melted using a hot-melt process. Chen instead teaches a transdermal system for delivery of ropinirole that comprises a laminated composite of a backing layer and a contact adhesive layer containing the drug. Chen, col. 3, lines 23–38. Chen fails to teach rotigotine, as admitted in the present Action at p. 6. Chen also fails to teach a cement matrix comprising a hot-meltable adhesive. Instead, the reservoir layer **12** (Chen, Fig. 1) is a pressure-sensitive adhesive that may be formed of various polymers, none of which is disclosed as hot-meltable. Chen, col. 8, lines 48–67. Chen still further fails to disclose partly or completely melting the active substance in the adhesive, and in view of the very high melting point of ropinirole (approximately 247°C), it is unlikely that melting this drug would be feasible in constructing a TTS. Chen, col. 2, lines 17–21. Moreover, Chen teaches use of solvents, including water and/or other hydrophilic solvents,

to dissolve the drug, which is expressly counter to present Claim 2. Chen, col. 9, lines 39–50.

Metman is provided for teaching transdermal delivery of rotigotine for treatment of Parkinson's disease. Metman, abstract.

Noel is provided for teaching a hot-melt silicone pressure sensitive adhesive (PSA) containing organic wax. Noel, abstract. Noel discloses that hot-melt PSAs are preferred over other adhesives because no solvents are required to coat the adhesive on a substrate, such as a bandage or patch. Noel, col. 2, line 66 – col. 3, line 1. Organic waxes include mineral waxes such as ozokerite and ceresine. Noel, col. 4, line 65 – col. 5, line 3.

Viewing the combination of Chen, Metman and Noel as a whole, the collective disclosures fail to teach or suggest a TTS formed using the presently claimed hot-melt process of mixing molten adhesive and partly or completely melted rotigotine. In fact, the combination fails to teach or suggest infusing or dispersing an active substance, whether ropinirole or rotigotine, into a hot-melt adhesive at all. In addition, Chen uses solvated ropinirole (dissolved in water or other solvent) mixed with a polymer to form a reservoir layer. This is at odds with Noel's preference for using a solvent-free composition and the benefits attributed to the hot-melt silicone PSA. It is not clear how a person of ordinary skill would reconcile these disparate teachings without contravening the operation of one of these references. See *In re Ratti*, 270 F.2d 810, 123 U.S.P.Q. 349 (CCPA 1959) (if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious). What is more, Noel simply discloses that the hot-melt silicone PSA is suitable for assisting in delivering a bioactive agent, such as a drug, but is silent regarding the present hot melt process where the active substance is partly or completely melted and dispersed in the hot-meltable adhesive. The combination of Chen, Metman and Noel consequently cannot establish a *prima facie* case of obviousness as the collective teachings fail to teach or suggest all of the features found in Claim 1.

The reference combination also fails to provide an apparent reason by which a skilled artisan would modify the collective teachings to include the missing subject matter. As noted above, it is not clear how a person of ordinary skill would reconcile the use of solvated drug in constructing a TTS (as in Chen) in combination with a silicone PSA that is preferred over other adhesives because no solvents are required (as in Noel). And, most notably, there is no

instance or even suggestion regarding partly or completely melting the drug for dispersal in a hot-meltable adhesive to form a cement matrix. Only the present application and claims appreciate the surprising result that rotigotine remains stable in admixture with molten adhesive without addition of stabilizers or antioxidants after the drug is melted. Present specification, paragraph **[0108]**. Finally, no reason based on the general knowledge in the art is identified in the present Action by which a skilled artisan would be led to include the missing subject matter. Independent Claim 1 and all claims dependent therefrom (Claims 2–16) are therefore nonobvious over Chen in view of Metman and Noel.

3.2. Claims 18 and 24

Claim 18 is drawn to a method for preparing a TTS that comprises a rotigotine-containing cement matrix. The method comprises melting and homogenizing components of the cement matrix (*i.e.*, the rotigotine and the matrix), solvent-free, in an extruder at a temperature between 70°C and 200°C prior to lamination of the components.

The combination of Chen, Metman and Noel, even if such combination can properly be made, which is not admitted herein, fails to teach or suggest melting rotigotine and components of the cement matrix and homogenizing the components in an extruder prior to lamination. As such, the combination cannot establish a *prima facie* case of obviousness. The reference combination further fails to provide any guidance for a skilled artisan in reconciling incorporation of a solvated drug, as taught by Chen, for use in the hot-melt PSA of Noel, which is preferably used solvent-free. There is no mention or reason identifiable in the collective teachings regarding melting rotigotine and homogenizing the components of the molten cement matrix in an extruder prior to lamination. Independent Claim 18 and Claim 24 dependent therefrom are therefore nonobvious over Chen in view of Metman and Noel.

3.3. Claims 20–23 and 25

Claim 20 is drawn to a method for preparing a TTS that comprises a rotigotine-containing cement matrix. The method includes pre-melting and homogenizing components of the cement matrix other than the rotigotine, solvent-free, in an extruder and introducing rotigotine at a temperature between 70°C and 200°C, into the pre-melted cement matrix.

The combination of Chen, Metman and Noel, even if such combination can properly be made, which is not admitted herein, fails to teach or suggest all of the claimed features and

accordingly cannot establish a *prima facie* case of obviousness. The references do not teach pre-melting and homogenizing components of the cement matrix other than rotigotine in absence of solvent using an extruder, and then introducing rotigotine at a temperature between 70°C and 200°C into the pre-melted cement matrix. The reference combination is devoid of any teaching or reason by which a skilled artisan would be led to include these several features. Independent Claim 20 and all claims dependent therefrom (Claims 21–23 and 25) are therefore nonobvious over Chen in view of Metman and Noel.

3.4. Rejection under 35 U.S.C. §103(a): conclusion

For reasons set forth above, a *prima facie* case of obviousness cannot be sustained for any of Claims 1–16, 18 or 20–25. Withdrawal of the present ground of rejection is respectfully requested.

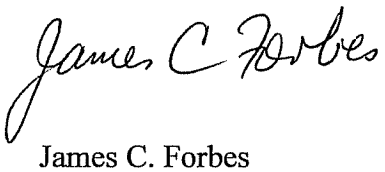
4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.



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